

5-1-1934

Acid base balance of the blood and its disturbance in disease

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ACID-BASE BALANCE OF THE BLOOD

and its

DISTURBANCE IN DISEASE

by

Arnold Irving Webman

Written in partial fulfillment
of requirements for the degree
of Doctor of Medicine, at the
University of Nebraska College
of Medicine, Omaha, Nebraska.

April 13, 1934

"Advances in scientific knowledge are
based upon speculative hypotheses
and the grain of truth they may
contain is only established
or disproved after dis-
appointment and toil
immeasurable."

-Harvey Cushing-

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I

P R E F A C E

The treatise on acid-base balance of the blood has been attempted on the merits of its originality among the many papers written as senior theses. However, in reviewing the literature on the subject, I discovered the reason for its unpopularity. It apparently requires extreme enthusiasm to write on a subject which is still, in part at least, in the domains of speculative medicine. It was a determination to interpret a theoretical and complex, biochemical problem into clinical medicine that made writing this paper a pleasant task.

I wish to thank Dr. H. B. Hamilton for suggesting the subject for my senior thesis. I am also grateful to Drs. Robertson and S. Mergulis for instructive comment on the subject.

April 13, 1934.

II

I N T R O D U C T I O N

Acid-Base Balance of the Blood

and its

Disturbance in Disease

It is exceedingly difficult to appraise properly the importance of any factor, influence or circumstance which operate in the well being of a living organism. The problem becomes even more complex when dealing with human beings. One must, therefore, conclude that each factor is only relative in its importance to some other factor, operating in unison for the maintenance of life and health. Disturbance of any one of these agents will directly or indirectly upset the existing balance, resulting in disease. Such a concept may likewise be applied to the acid-base balance of the blood.

The phenomena of acidosis and alkalosis, although representing a few of the apparently simpler problems of biological chemistry and physiology, has passed through numerous stages of erroneous concepts in the process of its development. At present, while much more clarified and crystalized, the concept of acid intoxication still remains, in part, at least, an unexploited branch of clinical medicine. The cause for its retardation in the practice of medicine is well described by Gamble (1928), who states:

----The knowledge gained (through research) often remains for a long time understandable only by those expertly experienced in the conception of physical chemistry and in the mathematical method of ascribing

the interdependence of the factors involved. This is very unfortunate, since the application of such knowledge to the control of disease must be understandable by practitioners of medicine, who cannot be expected to have a facile knowledge of the terms of chemistry and of higher mathematics. The theory of this type of research ought to be translated in plain English.

It is with such sympathy and understanding----that I have attempted to discuss a subject of specialty. It is the chief aim of this treatise:

1. To emphasize the extreme constancy of reaction in the living body.
2. To emphasize the lability to change in reaction in infancy and childhood as a result of disease.
3. To correlate normal function with the corresponding disturbance as found in certain diseases, and,
4. To apply a rational form of treatment in order to readjust the upset acid-base balance.

The paper is especially directed toward a critical discussion related to the rationale of alkali therapy. It is obvious that only a limited number of conditions can be considered in a treatise of this type.

Again, in order to fully review the subject of acid base balance, other factors such ^{as} mineral and water metabolism, osmotic and onkotic pressure, as well as the still mysterious hormonal influences need be considered. Since the problem under which title I present this ^{treatise,} is already complex, per se, I shall be forced to omit a discussion of related factors.

Finally, the reader should be convinced by the fact that acidosis and alkalosis are merely symptoms of pathological phenomena. Each form of acidosis, for example, may have a different cause, whose origin and course we are attempting to solve. It is only through such analysis that a logical form of treatment can be instituted.

The reader will no doubt be aware of the fact that acidosis has been treated to a greater extent than alkalosis. This is only natural in view of the greater frequency of acidosis in certain diseases of infancy and childhood.

III

H I S T O R Y

According to Folin (1907), the theory of acid intoxication had its inception with Bonsingault, who in 1850, was first to discover large amounts of ammonia in the urine of diabetic patients. He claimed to have found the mechanism by which excessive acid production in the body is regulated. Hallerworden in 1880 confirmed such findings. He also showed that ammonia in the urine grew less, when alkali drugs were administered. He concluded that the ammonia acts as a "factor of softy" in body metabolism. He believed that the production of ammonia took place in the kidney, liver and related organs, and was directly related to protein metabolism. It may be of interest to note that half a century later and in the midst of rigid experimental research, not much more can be added to this concept.

Ewing (1908) awards credit to Stadelman with the discovery of beta-oxybutyric acid in diabetic urines. In the same year R. von Jaksch (1883), showed that the Gerhardt's ferris chloride test, still in use today, is positive in diabetic and in certain febrile urines. He referred this color reaction to the presence of diacetic acid. He concluded that the diacetic acid as well as the beta-oxybutyric acid are responsible for the symptoms present in severe diabetes. Thus the term acid intoxication, or "acidosis" was first taken to mean an accumulation of acetone bodies in the urine, and practically synonymous with severe diabetes.

Walter (1877) has recognized, however, symptoms of acidosis in non-diabetic patients. He thus studied the problem

from a new angle. He showed that administration of 0.9 gram or over of HCl per kg. body weight would prove fatal in rabbits, although the serum remained neutral or even slightly alkaline to litmus. He roughly measured the CO_2 concentration of the blood and found that in the fatal cases it dropped to 2 or 3 vols. per cent, as compared with 45 to 50 vols. per cent in normal rabbits. His work has been confirmed by numerous workers, including the more recent experiments of Gamble and Ross (1923).

The work of Walter proved of great significance in the development of the acid intoxication theory, for it points toward a compensatory mechanism in the blood itself in an effort to maintain a normal acid base balance of the body. It was not until a better laboratory technique was developed that the actual mechanism involved could adequately be studied.

Zuntz (1865) noted that when blood is exposed to an increasing concentration of CO_2 the NaHCO_3 in the true plasma is increased, while the NaCl concentration is reduced. He interpreted this behavior of the blood as being due to a migration of alkali originally in combination with hemoglobin into the plasma as NaHCO_3 .

Gürber (1895) showed that there is no actual migration of alkali out of the corpuscle, but a redistribution between corpuscles and plasma of anion. Moreover, he showed that the decrease in NaCl noted is due primarily to a migration of chloride ion into the cell, decreasing the acidity of the plasma. Gürber's idea has been confirmed by many workers.

Van Dyke and Cullen (1917), however, were able to account for only 72% of the alkali increase of the plasma on the basis of the chlorine shift. They believe that acid ions such as $\text{SO}_4^{=}$ $\text{PO}_4^{=}$ are also capable of such migration, accounting for the balance increase (28%) of alkali in blood plasma. Similar results were obtained by Doisy, Eaton, and Chouke (1922).

The researches of L. J. Henderson (1909, 1920, 1921), first gave a clear conception of the acid-base balance in the animal body. Since that time an immense amount of work has been done in this field, notably by Van Dyke (1921). Marriott and Hartmann (1916, 1928), and many others. The work of these men will be the guiding principle of this treatise.

IV

N O R M A L P H Y S I O L O G Y

The reaction of any solution depends upon the number of H-ions and OH-ions it contains. In neutrally reacting water the two types of ions are equally strong, each being 10^{-7} at 22°C and $10^{6.8}$ at 37°C . A most important property of aqueous solutions is that the concentration of H-ions and OH-ions are so related to each other that the product of the two is equal to a constant K_w . The formula may be expressed as:

$$[\text{H}^+] \times [\text{OH}^-] = K_w^{(1)}$$

Thus, an increase in the $[\text{H}^+]$ is necessarily accompanied by a decrease in the $[\text{OH}^-]$. Similarly, a decrease in the $[\text{H}^+]$ is associated with an increase in the $[\text{OH}^-]$.

Human blood with its feeble alkaline reaction has a $[\text{H}^+]$ of $10^{-7.35}$ to $10^{-7.45}$ or an average of $10^{-7.4}$ (Austin and Cullen, 1926). Instead of citing the H-ion figure, one frequently speaks of the logarithm of that number. This is called the H-ion exponent, and is expressed in pH. Thus, if $[\text{H}^+] = 10^{-7.4}$, then $\text{pH} = (-7.4) = 7.4$.

Henderson (1909) has emphasized the fact that the constancy of the reaction of the blood is even more carefully guarded than the other great constants of the body such as temperature and osmotic pressure. Hence, slight changes in the H-ion concentration of the blood determines the border line. The importance of a thorough understanding of the mechanism of such changes becomes obvious.

Note: The brackets refer to the concentration of the ion in a given solution.

Some idea of the narrow range of this reaction in the blood may be obtained if one considers that death may result if the blood shifts for any length of time to the acid reaction represented by distilled water, or on the other hand by the alkali reaction of tap water (Schultz, 1933). The phenomenon becomes still more interesting, almost miraculous, when we consider the large overproduction of acids in the normal blood as a result of metabolic processes, without varying the pH of the blood to but a small fraction of one per cent.

According to Anderson (1908), carbon dioxide is constantly formed in the normal individual as an end product of protein, fat, and carbohydrate metabolism. Sulphuric acid is formed in the process of catabolism of certain amino acids (cystine). Phosphoric acid is derived from nucleic acid and lecithin. Organic acids are derived from the intermediary metabolism of fatty acids, deamination of amino acids and incomplete oxidation of glucose.

Due to the complexity of the mechanism involved in the maintenance of a constant acid base balance, a detailed discussion of each factor would be appreciated only by the specialty on the subject. Morgulis (lectures, 1931) has well outlined the subject on basis of chemical, mechanical, and physiological behaviorism. But even this method of approach is a difficult one, for each of these factors cannot be considered alone.

Hartmann (1929) recognized three chief factors which directly or indirectly regulate the pH of the blood. These may briefly be outlined as follows:

I Buffer Action

II Respiratory Activity

III Renal Activity

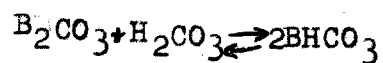
Buffers are complex substances-weak acids and their alkali salts-which are able to neutralize acids or bases so that the reaction of the system as a whole is not changed or very slightly so.

According to Lewis, carbon-dioxide exists in four forms, he lists them as:

1. Free anhydrous carbon-dioxide (CO_2)
2. Carbonic acid (H_2CO_3)
3. Bicarbonate(BHCO_3)
4. Carbonate (B_2CO_3)

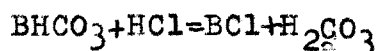
where B is used to represent a monovalent base such as K or Na.

In reality only the 2nd and 3rd exist in the blood to any appreciable extent, since free CO_2 forms carbonic acid when in solution and the bicarbonate will react with the carbonate as follows:

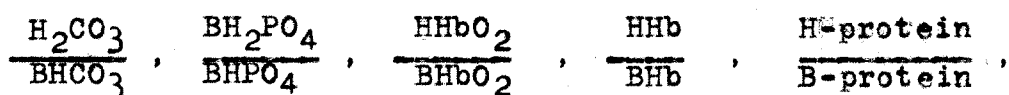


Hence, only H_2CO_3 and BHCO_3 exist in the blood. Such a solution containing an acid and an excess of alkali salts in a definite ratio is called a "buffer" solution, because it has buffer action, to resist rapid change in hydrogen ion concentration. To give a mathematical interpretation of such action would be beyond the scope of this treatise. Suffice to say that its buffer action depends on the slow ionization of the carbonic acid, so that addition of strong acid to such a solution would convert the salt

of the weak acid into more of the weak acid, thus removing H-ions from the solution. The reaction may be represented as follows:



The weak acid, may be excreted by the lungs (in case of H_2CO_3) or by the kidneys, depending whether or not the acid is volatile. Bodansky (1926) has outlined a set of buffers present in normal blood.

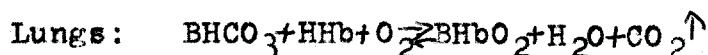


where B is any monovalent base, HbO_2 represents oxyhemoglobin, and Hb- reduced hemoglobin.

The action of phosphate as a buffer lies in its ability to change from the alkaline dibasic phosphate (B_2HPO_4) to the diacid phosphate, the latter being excreted through the kidney, hence removing acid from the system. However, Jones and Nye (1921) have shown that blood plasma contains 9.5 mgms. of H_3PO_4 per 100cc of plasma or about 0.001 mole. They conclude that phosphate have a negligible effect on the hydrogen ion concentration of normal blood plasma. Similar deductions have been made with regard to the buffer effect of protein (Medical Research Council, 1923). Henderson (1908) calculated the buffer value of proteins in plasma and came to the conclusion that this amounts to but only a small fraction of the whole buffer effect of the plasma, except in dehydration where the protein plays an important role (Fischer, 1926). Normally, however, it is the bicarbonate and hemoglobin that furnish the greatest percentage of buffer action. Both of these substances are closely associated with the second factor noted by Hartman - the respiratory mechanism.

It has been long noted that when acid is added to blood in vitro, a slow rise of the H-ion concentration takes place. In the living organism, however, an equal quantity of acid does not provoke such a change (Roscher, 1933). Obviously, there must be other factors aside from the buffer action of the blood to prevent this change in pH.

Changes taking place in the lungs and hemoglobin are rapid. Such rapidity of action becomes necessary when one realizes the rapid production of CO_2 in tissues which must be eliminated. Oxy-hemoglobin being a stronger acid than reduced hemoglobin has a greater ability to hold on to base. Such base together with oxygen (BHbO_2) is carried from the lungs to the tissues of the body for oxygenation. As the oxygen of the hemoglobin is given off, the latter becomes more alkaline, thus releasing the base for the union with carbonic acid ($\text{CO}_2 + \text{H}_2\text{O}$) just being given off by the tissues. As the reduced hemoglobin and the base bicarbonate travel through the lung, the former becomes oxygenated, hence more acid, and is able to take the base from the bicarbonate - which, in the increased pH of the medium is decomposed into CO_2 and water. The CO_2 is then given off by expiration. Austin and Cullen (1926) represented the process in the tissues and lungs as follows:



By this mechanism, not only is the ration of $\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3}$ kept constant (within a pH range 0.03), but also the transfer of oxygen is made possible.

The quantity of free CO_2 in the blood depends on the carbon dioxide tension in the lungs. In case of a normal carbon dioxide tension of 42 mm. Hg., the free CO_2 in the blood amounts to 3 vols per cent. The quantity of CO_2 which can be dissociated in vacuo - as regards plasma by addition of acid - amounts to about 55 vols. per cent (Roscher, 1933). Thus, the amount of physically dissolved carbonic acid in proportion to the bound carbonic acids in (as salts, mainly as BHCO_3) is 3 to 60 or 1 to 20. This is equivalent to the ratio of $\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3}$, the original "buffer" discussed above.

The above principle is used in determining the pH of the blood, for a change in this ration is paralleled by a corresponding change in the pH. The ratio can be displaced in the direction of an increase quantity of H_2CO_3 partly by an increase of the CO_2 production and partly by the dissociation of CO_2 from Na HCO_3 through the action of acids formed as a result of metabolism in the body. Moreover, NaHCO_3 may be lost through excretion by way of the bowel (Howland and Merriott 1916), or kidney. Such changes would tend to decrease the pH of the blood.

On the other hand, an increase in the pH will tend to increase the pH of the respiratory center (Austin and Cullen, 1926), stimulating increased respiration. This would tend to hasten the excretion of CO_2 , until the ratio of $\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3}$ again becomes normal. Conversely, an increase of the bicarbonate or a decrease of CO_2 in the blood may be compensated by a decreased respiration. This takes place through a decreased irritation (depression) of the respiratory center, until the ratio of $\frac{\text{acid}}{\text{base}}$, hence the pH, is again brought to a normal value.

The role the kidney plays in the maintenance of an acid-base balance will be obvious from a study of its normal physiology. It is the chief excretory channel of metabolic waste products. According to Hartmann (1929), the kidney has two functions in regulating the pH of the blood.

1. By regulating the urinary pH
2. By substituting ammonia for "fixed" base

The normal kidney, according to Hartmann, is capable of secreting urine as acid as pH5, or as alkaline as pH8. It has the ability to excrete the acid or base phosphate, depending on the relative concentration and pH of the blood. At a pH5 considerable amounts of the weaker organic acids are excreted unneutralized (about 5% diacetic and 20% beta-oxybutyric, etc.) while phosphate in the form of monobasic salts and BHCO_3 are almost absent (Gamble, Ross and Tinsdall, 1923).

In addition to fixed base economy, in times of need, by regulating acidity, the normal kidney also has the ability to manufacture ammonia. This is formed from the incomplete metabolism of protein, that is, the split products of protein metabolism (amines) do not reach the end stage (urea) but stop short in the process, forming ammonia. This is said to take place in the kidney, but other tissues as the liver may likewise be involved (Morgulis' lectures, 1931). The ammonia acts as a substituted product for fixed base bound to acids coming to the kidney for excretion.

In summarizing the mechanism through which a normal acid-base balance in the blood is maintained, the following factors

need be mentioned:

- I The "Buffer" action of the blood
 - A - The buffer salts
 - B - Changes in the base binding power of hemoglobin and oxyhemoglobin
 - C - The "chlorine shift."
- II Respiratory activity
- III Renal activity
 - A - Regulation of urinary pH
 - B - Substitution of ammonia for "fixed" base

The effect of the "chlorine shift" on the pH regulation of the blood may be inferred from the work of Doisy, Eaton and Chonke (1922). They have estimated that when the reaction of the blood is changed from pH7.45 to pH7.25 by the absorption of carbon dioxide, the base furnished to form the additional plasma bicarbonate comes from the following sources:

1. Due to non migrating serum buffers ----- 16%
2. Due to migration of chlorine ion into corpuscles --- 80%
3. Due to migration of ther acid radicles ----- 4%

V

PATHOLOGICAL PHYSIOLOGY

According to Austin and Cullen (1926), the term a c i d o s i s and a l k a l o s i s, common in clinical usage, are often used by different individuals to describe entirely different conditions. This is probably due to the fact that acid intoxication was first associated with diabetes and recognized as an accumulation of abnormal acids, diacetic, beta-oxybutyric acid and acetone, in the blood. Hence, "acidosis" has been used to describe either a ketonemia or a ketonuria. With the gradual recognition of a disturbed acid-base balance in non-diabetic conditions the term a c i d o s i s has been given a number of definitions, many of which do not seem to apply adequately to the conditions involved.

Sellard (1912) defines "acidosis" as a symptom complex, attributed to excessive production of acid acting principles in the blood. "He, as well as many other authors applied the term to a number of conditions, such as acetonuria, acetonemia, decreased alkali reserve, decreased carbon-dioxide tension of alveolar air, and to a decrease in the pH of the blood plasma. The objection to any of these conditions is that none of them specifically describe the pathological disturbance present within the body.

Van Slyke and Cullen (1917) emphasized that the content of bicarbonate of the blood was essential for acid-base balance and defined a c i d o s i s as "a condition during which the amount of the bicarbonate content of the blood, i.e., the alkali reserve had decreased below normal. They also pointed out the difference between ketonuria and acidosis, showing how the ketone bodies will effect the alkali reserve.

Of the various attempts to establish a more precise terminology, none were as successful as Van Slyke (1921). In considering the normal and abnormal variations in the acid-base equilibrium of the blood, he showed that nine conditions are theoretically possible. The blood bicarbonate may be high, low or normal, and in each of these cases the pH may be high, low or normal. Only that condition is normal in which both the bicarbonate and the pH are within normal limits. He thus presents nine possible variations, eight of which are pathological conditions, either acidosis or alkalosis. It would be beyond the scope of this treatise to describe each condition separately. Space permits but a list of these possible variations, they are as follows:

- Area 1. Uncompensated alkali excess.
- Area 2 & 3. Uncompensated CO₂ Deficit
- Area 4. Compensated alkali or compensated CO₂ excess.
- Area 5. Normal acid-base balance.
- Area 6. Compensated alkali deficit or compensated CO₂ deficit.
- Area 7 & 8. Uncompensated CO₂ excess.
- Area 9. Uncompensated alkali deficit.

His list of possible variations emphasizes the fact that the best method of expressing the condition as it actually exists in the blood is to report the pH and bicarbonate content of the plasma. The methods used to determine such values, directly or indirectly willsoon be considered in brief.

It becomes obvious that an abnormal function of any of

the chief agents already noted would necessarily result in a disturbed acid base ratio. It should also be apparent that with every increase of acid in the body, there is a corresponding reduction of base, i.e., a depletion of the alkali reserve in the body. If this condition is to continue the ratio of acid base would be greater than 1:20, and a corresponding increase in the H-ion concentration (lowered pH) would follow. But like many other physiological processes, minor abuses are taken care of by a compensatory mechanism. As in the case of the heart, kidney, etc., we have a c o m p e n s a t e d acidosis, a term originally proposed by Van Dyke to a condition where the alkali reserve has been partially depleted, but due to the greater elimination of CO₂ by the lungs and of other weak acids by the kidneys, the ratio of acid base will still be the same. An uncompensated acidosis is, of course, a condition where acid is not proportionally excreted, resulting in a fall of bicarbonate (alkali reserve), or of pH or both.

Similarly, an increase in the alkali reserve, an alkalosis, can also be compensated or uncompensated, according to the amount of carbonic acid showing a corresponding rise or fall..

It should be clear from the discussion above, that an increase of carbonic acid in the blood, or a decrease of the alkali reserve, per se, is no reliable proof of the existence of an acidosis, nor does an increase in the quantity of acid influence the pH of the blood, if the acidosis is compensated. Moreover, in order to determine the amount of deviation in the acid-base balance of the blood, both CO₂ and bicarbonate values must be measured.

The post mortem findings in acidotic conditions varies, of

course, with the specific disease under consideration. The classical work of Minkowski (1886) with regard to the physiology of the liver has shown, among other things, that the liver aids in maintaining a normal acid base balance, through its ability to produce ammonia from urea. That this is now what actually occurs in the liver has already been noted (p11). Grile (1915a, 1915b) firmly believed that both the liver and adrenal gland directly or indirectly influence the acid base balance of the blood.

Changes, due to acidosis has been noted in the liver, spleen, and central nervous system (Ewing). Such changes, however, may have been a result of the etiological factor and not to the subsequent acidosis.

VI

D I A G N O S I S

Kussmaul (1874) was first to note an alteration in the rate and depth of respiration in severe diabetic acidosis. In his classical description, he relates:

1. The characteristic form of dyspnea, g r o s s e A t m u n g -- the very deep, regular and somewhat accelerated respirations, 20-40 per minute, with a lack of venous congestion.

2. Nervous excitation, screaming, hypogastric pain.

3. A rapid weak heart, 120-140 per minute. Kussmaul concluded that this form of coma was caused by a direct stimulus of the respiratory center, by some intoxication arising in the course of the disease and not from the loss of oxygen or accumulation of CO_2 .

As stated by Ginsburg (1933), the patient may convey an impression of one who is suffering from some cardiac or pulmonary defect, but he is not cyanosed, because there is no increase of CO_2 in the blood (in diabetic acidosis). On the contrary the CO_2 in the blood is diminished (Gamble, 1928). The lungs are absorbing plenty of oxygen from the atmosphere and the heart distributes it through the circulation at a sufficient rate, but it cannot reach the tissues, because of the CO_2 accumulation. As a result of this insufficient nourishment the nervous system is first to suffer, and its highest faculty - consciousness is abolished. The patient has thus entered into a state of coma.

McCrossin (1928), listed a number of common findings in acidosis. He noted; "irritability, nervousness, headache, weakness, nausea and perhaps vomiting, stupor or somnolence,

increased air hunger of Kussmaul type, lack of cyanosis, flushed face and red lips." He also states that in case of dehydration the tongue is a good "barometer" of the condition of the patient. "If the whole surface of the tongue is dry the patient will be in coma within an hour." Sellard believed that a Kussmaul type of respiration in the absence of any pulmonary pathology is very diagnostic of acidosis.

All workers on the subject agree that a diagnosis of acidosis is not complete without laboratory verification. Moreover, it is pointed out by Van Slyke and Cullen (1917), Roscher (1933), and many others that only quantitative determinations of both blood and urine will render a diagnosis complete. This procedure would involve a determination of the CO_2 content and CO_2 capacity (alkali reserve) of the blood, and would give not only the pH $\left(\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3} \right)$ ratio, but also the bicarbonate value (Roscher).

Sellard (1912) has shown that the administration of 3-5 grams of sodium bicarbonate to normal individuals was sufficient to render the urine alkaline in reaction. In a series of cases of Asiatic cholera with renal complications the patients developed a great tolerance for sodium bicarbonate; the urine frequently remained acid after intravenous injections of 30-60 and even 100 grams of the alkali salt. He corroborated these findings with laboratory examinations and found a lowered pH of the blood in almost all of these cases. He thus concluded that this increased tolerance represents essentially a deficit

in bas, id est, it constitutes an acidosis.

On the basis of the above observation he proposed to used the bicarbonate not only as a therapeutic measure, but also to indicate the degree of acidosis. An increased tolerance to the base would signify an increasing acidosis. This became known as the Sellard Test, and has been faithfully recommended by many clinicians as a test for acidosis, as well as a therapeutic agent. Similar results were obtained by Palmer and Henderson (1913). In a series of uremic cases, some of their patients received as high as 112 grams of bicarbonate but still excreted an acid urine. They concluded that the kidneys excrete an alkaline urine only where the bicarbonate content of the blood reaches a certain level.

Palmer and Van Dyke (1919) in a series of studies in acidosis set out to determine the validity of Sellard's test. They found that a fairly definite level of plasma bicarbonate normally exists, at which the urine changes from the more acid to the more alkaline than the blood. But no definite level could be obtained in pathological cases. Moreover, they emphasized the danger of giving unnecessary amounts of bicarbonate, when continued until the urine turns alkaline. Their results show the necessity for carefully controlled use of alkalies in therapy. They further state:

As a diagnostic measure for acidosis, Sellard's test is subject to certain errors especially in pathological cases, acting to make the results indicate a more severe acidosis. Blood analysis is, therefore, the best test.

Based on the weight of the individual and alkali deficit, they constructed a guide to dosage of alkalies.

T a b l e

Wt. of Individual		Sod. bicarb. necessary to raise plasma bicarb. 1 Vol. %
<u>Kg.</u>	<u>lbs.</u>	<u>Gms.</u>
19	42	0.5
38	84	1.0
57	126	1.5
76	168	2.
95	210	2.5

The methods which have been used in studying the pH of the blood may be divided into two main groups:

I The direct method

A - The hydrogen electrode

B - The Indicator method

II The indirect method

A - Determination of free and "fixed"
carbonate

B - Alveolar CO₂ tension

By the first method, the pH of the blood is measured directly. The principle of the hydrogen electrode has been described in detail by Clark (1920-22). Determination by the indicator method, the blood is centrifuged and a definite amount of neutral red is added to the plasma. The color formed is matched with that of standard phosphate solutions containing neutral red. This method was first proposed by Bayliss (1919).

A similar method has been proposed by Levy, Rowntree and Marriott (1915). A blood dialysate is compared with standard

color of known pH. The ratio free to fixed carbonate in the dialysate obtained is the same as in the blood plasma/ This method is superior to the hydrogen electrode method, due to its greater speed and accuracy in determining the pH of the blood. It is apparent that the direct method gives no idea of the alkali reserve (BHCO_3) of the blood. Moreover, the percentage of error is too great to be excepted as a method for routine work.

The indirect method involves the determination of the free and fixed H_2CO_3 . From this determination the pH of the blood may be calculated by the formula

$$\text{pH} = \text{pK} + \log \frac{\text{Base}}{\text{Acid}}$$

The most reliable method of determining the free and fixed carbonic acid is that used by Van Dyke and Cullen (1917). Their method consists briefly in withdrawing oxalated blood from the vein of an arm without stasis or loss of CO_2 , centrifuging at once and pipetting of the plasma. This plasma is then brought into equilibrium with the alveolar air of the observer at room temperature, and the CO_2 content estimated by the Van Dyke apparatus (Van Dyke and Neill, 1924). The percentage volume of CO_2 obtained after correction and subtraction of the CO_2 dissolved, gives the alkali reserve of the plasma. The technique in carrying out this determination with recent modifications is well described by Gradwohl (1928).

This method gives us the bicarbonate content of the blood plasma at a standard pressure of CO_2 of 40 mm. of Hg. - the normal alveolar CO_2 pressure. In normal individuals bicarbonate

plasma varies between 55-65 vols. per cent, using arterial blood for the test. An alkali plasma below 40 vols. per cent indicates an acidotic condition.

Since the alveolar CO_2 is in equilibrium with the free CO_2 of the blood, the latter can be estimated from the former. The usual method employed for ascertaining the alveolar CO_2 pressure by direct observation, depends on the fact that the last portion of a deep expiration consists of alveolar air. The last portion is collected and analyzed. Numerous modifications in technique have been adopted, but the principle involved in each is the same (Medical Research Council, 1923).

A reduction of the alveolar CO_2 pressure should indicate an increase in the fixed acids of the blood, hence an acidosis. This method does not, however, show whether or not the apparent acidosis is compensated (by a proportional increase of fixed carbonic acid) or not. The latter can be determined only by the Van Slyke method, noted above.

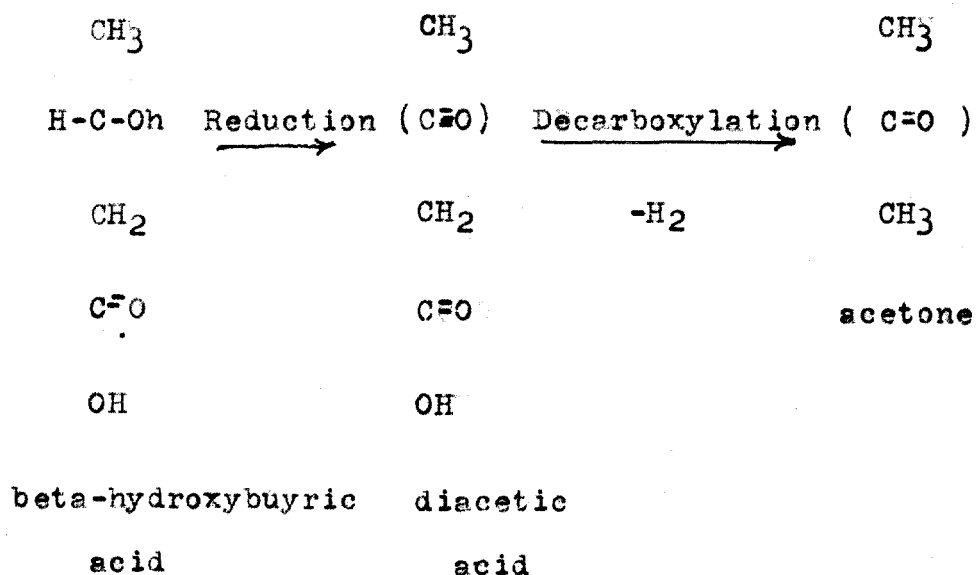
One should keep in mind the possible errors involved in determining the free carbonic acid of the blood by measuring the alveolar carbon dioxide tension. In certain heart diseases, as a patent foreamen ovale or any condition whereby venous blood is short-circuited, an admixture of venous and arterial blood in the radial artery will not be proportional to the carbon-dioxide tension of alveolar air. Again, in shallow breathing, common in many pathological conditions, a true sample of alveolar air is often difficult to obtain, and in turn the alveolar CO_2 determination will be too low (Medical Research Council, 1923). Such conditions should be recognized and accounted for.

Supplemented information for judging compensated or uncompensated deviations of the acid-base balance of the blood may be gotten by examining at the same time the amount of free acid, ammonia and of base contained in the urine. According to Roscher (1933), a compensated acidosis with a low CO_2 content in the blood, but where the pH is normal will manifest itself in the urine by increased excretion of free or bound acids. The urine findings will thus tend to confirm the supposition of a compensated acidosis which a low carbon dioxide content may give in case of a normal pH.

VII

D I A B E T I C K E T O S I S

That acidosis of diabetic origin is due to an accumulation of ketone bodies in the blood was noted as early as 1857 by Peters. He was first to detect acetone in the blood and urine of diabetic patients. Gerhard in 1865 showed that in the severe diabetic, the urine besides acetone, also contains diacetic acid which is responsible for the characteristic reaction with ferric chloride (Gerhard's test). Stadelmann in 1883 showed the presence of beta-oxybutyric acid in the blood and urine of diabetic patients. One year later Minkowski showed the close relationship between beta-oxybutyric, diacetic acids, and acetone. He named this group "ketone bodies," since two of these substances, both of which are derived from beta-oxybutyric acid contain the ketone grouping:



That a disturbance in the acid-base balance of the blood existed in diabetes was recognized by many of these early workers but the term "acidosis" was used to describe a ketonemia, or an abnormal accumulation of these acetone bodies in the blood.

Hence "acidosis" had its beginning in diabetes, although it soon involved other conditions.

Ketone bodies represent split products of fatty acids and to a certain degree of amino acids. The origin of ketone bodies has by no means been definitely agreed upon. It is held that during normal metabolism these intermediary products of fat and protein metabolism are burned to carbon-dioxide and water. For such a transformation carbohydrate in sufficient quantity is required. If carbohydrate is lacking, as in the case of a disturbed carbohydrate metabolism, the ketone bodies are not transformed anymore and accumulate in the body leading to a ketonemia and ketonuria (Hartmann, 1929).

The conclusion reached with regard to fatty acid metabolism is the result of numerous investigations, far beyond the scope of this treatise. Only a few of the "high-lights" can be mentioned here.

Geelmuyden (1904) suggested that ketone bodies enter into union with certain split products of carbohydrates, this union being necessary for the further combustion of the fatty acid molecule. This was later confirmed by Woodyat (1910).

In more recent work, Geelmuyden (1923) shows that the antiketogenic effect of carbohydrates is a function of the amount of glycogen stored in the liver. He does not consider ketone bodies as mere split products of fat and certain amino acids, but that they likewise represent intermediary products in sugar

synthesis of fat. He also emphasizes the depletion of glycogen from the liver, with subsequent displacement of fat in that organ. This is followed by a lipemia-what he calls -"fat wandering". According to his conception, the organism due to fat wandering attempts to synthesize sugar for the combustion of fat, but stops short in its attempt, giving only intermediary products, represented by ketone bodies. Parallel with this fat wandering is an increased metabolism of albumen with attempts on the part of the organism to form sugar from protein as well.

Roscher (1933) emphasizes that only beta-oxybutyris and diacetic acids accumulate in the blood in cases of ketonemia, while acetone is formed from these acids in the bladder and is then reabsorbed into the circulation. Part of the primary acids excreted, are thru the kidneys, escapes thru the lungs as acetone. The balance unite with alkalies of the blood, depleting the alkalies of the blood, depleting the alkali reserve. At this stage the body begins to build a new line of defense by the increased production of ammonia for neutralization of these acids. This process is an "alkali sparing" device on the part of the body. The ammonia is derived from incomplete protein metabolism, that is the amine group does not reach the stage of urea production (Lewis, 1929).

In advanced stages of diabetes, as the tolerance for carbohydrates grows less and the fat metabolism becomes poor, the ketone bodies accumulate to a still greater extent in the body,

so that the compensatory effect of the ammonia does not suffice to neutralize them all. They will then unite with the alkali metals to such an extent that there are not enough left to carry the carbon dioxide from the tissues to the lungs for elimination. Hence the carbon dioxide remains in the body tissues, and thru its increase in the respiratory center will stimulate respiration leading to the Kussmaul type of breathing (Y. Henderson & A. Greenberg, 1933).

The clinical picture of diabetic coma is described in every textbook of medicine and need not be reviewed here. Suffice to say, that the patient may convey an impression of one who is suffering from pulmonary or cardiac pathology, because of the marked dyspnea. The clinical picture of diabetic ketosis has already been given (p. 22). Suffice to say that the hyperpnea is not due to the lack of oxygen, but to the accumulation of acids in the tissues, preventing oxygen exchange.

But this is only part of the picture in diabetic acidosis. It has long been known that as the ability to oxidize glucose diminishes, hyperglycemia develops, followed by glycosuria. Excretion of large amounts of glucose requires an increased quantity of water. This is compensated by the polydypsia and subsequent polyuria presented by these patients. Hartmann and Darrow (1928) found that the plasma in diabetic acidosis may become very concentrated. But despite such anhydremia, the concentration of total base tends to be slightly below normal the lowest value being 133mM. Both bicarbonate -

n a t e and c h l o r i d e are diminished relatively more than ketone acids and proteins are increased. Loss of BCl and BHCO_3 is a compensation for the hyperglycemia, thus keeping the osmotic pressure within normal limits.

In the extreme case of diabetic coma the loss of BCl and BHCO_3 is still greater, dehydration occurs, regardless of the amount of water intake. If vomiting becomes marked there will be an added reduction of fluid and minerals in the form of gastric and intestinal secretions. As a result dehydration and particularly enhydremia may become extreme and lead to desiccation and death.

Gamble (1928) did not find a decrease in the total base, but a marked increase in ketone acids which depress the bicarbonate (alkali reserve) and thus lessen the pH. His diagram (No. 7) was constructed from the blood picture findings of a child entering the hospital in diabetic coma. The area designated K in the diagram, representing the concentration of ketone bodies, shows how extensively these acids replaced the bicarbonate in the plasma. He does however, believe that base and chlorides may be lost when vomiting accompanies the disease. The difference in their findings may also be explained by the fact that Gamble explained only one possible condition in diabetic coma while Hartmann and Darrow studied the blood picture in a series of cases under varying conditions.

The discrepancy in the findings of Gamble and that of Hartmann and Darrow, is of great significance. For if bicarbonate alone is depressed through the increase of ketone bodies, the administration of insulin, glucose and water should clear up the ketosis and replace fluid lost. On the other hand, if base chlorides and base bicarbonate is also lost, such electrolytes must be replaced by the addition of minerals and alkali solutions to the above form of treatment.

Hartmann and Darrow in the same series of investigations have tried to study the effect of salt solution, alkalies, glucose, insulin and water in various combinations. Their results are extremely interesting. They have shown that when therapy consists of the administration of water and insulin with or without carbohydrates, the base bicarbonate and pH are restored relatively v e r y s l o w l y . In interpreting their results they claim that as the ketone salts are being oxidized they furnish base which is claimed first by other acids chiefly by the chlorides, less so by phosphates and proteins.

The newer knowledge with regard to the etiology of diabetes, and the subsequent introduction of insulin, alkali therapy was practically cast out of use in diabetes. One of the most impressive action of insulin is afforded by the changes in diabetic acidosis following insulin treatment. This has been first shown by Cullin and Jonas (1923). A patient with a plasma pH of 6.98 and a base bicarbonate concentration of 16 vols. per cent had his plasma restored in one day to a normal range with a plasma pH of 7.32 and a base bicarbonate concentration of 41.5 vols. per cent. The insulin altered the metabolism so that not only did

further accumulation of ketone bodies cease, but also those that were combined with base were oxidized, freeing the base to recombine with the carbonic acid released from the tissues, increasing the alkali reserve of the blood. Moreover, they show that increased use of insulin may raise the pH of the blood to such an extent as to develop an alkalosis and tetany. Subsequent work by many noted investigators has been in full agreement with their findings. A thorough review of the subject of insulin therapy has been given by Campbell (1933).

It would thus appear that insulin treatment alone, without alkali is sufficient to restore acid-base balance in diabetic acidosis to a normal state or even to an alkalosis. That other factors enter in, such as an excessive loss of water and with it a loss of electrolytes in the form of NaCl and NaHCO_3 has been conclusively shown by Hartmann and Darrow. Hence two chief factors must be taken into consideration in the treatment of diabetic acidosis (1) the role of ketosis and (2) the role of dehydration, and electrolyte depletion in the more severe cases.

Based on such a conception of pathogenesis of diabetic acidosis, a rational form of therapy, in the ordinary "uncompensated" diabetic acidosis, where the pH of the blood plasma has been reduced only slightly would be directed toward abolition of the ketosis. This would resolve itself in the establishment of adequate balanced diet, with the frequent use of insulin. The type of diet, would depend on the age, weight and tolerance of the patient for glucose. Insulin would be indicated in these cases to prevent a ketosis and ketonuria (Campbell, 1933). The details of this method of treatment is beyond the scope of this

treatise and may be found in any good textbook.

In cases where both factors are involved, that is where there is present a faulty glucose and fatty acid metabolism, along with dehydration, (noted by clinically by the dry skin, dry tongue) marked loss of electrolyte and reduced pH of the blood plasma the logical form of treatment should according to Hartmann(1929) include the following:

1. "Very rapid or immediate relief of increased acidity in those cases in which acidosis is extreme and death is feared.
2. "Complete restoration to normal of altered electrolyte water, and total osmotic concentration of the body fluids, which includes,
 - a) "Addition of electrolyte, especially NaCl and NaHCO_3
 - b) "Reduction of glucose
 - c) "Abolition of ketosis

He feels that although restoration of NaHCO_3 , and consequently pH, of the blood may be accomplished by glucose oxidation thru insulin administration, such relief may be too slow to prevent death in the most severe cases. A protocol of one of the cases so treated is given under case reports. It must be emphasized that they do not recommend continuous, careless use of alkali and salt, but only in the extreme cases of diabetic ketosis.

This new concept, of alkali usefulness, has been verified by many authors. Campbell (1933), although extremely enthusia-

stic with the use of insulin, favors the additional measures advocated by Hartmann and Darrow. McCrossin (1929)), believes that it is more difficult to reclaim patients who have been days or weeks getting into a semicomatose condition, than it is to revive one who has suddenly precipitated into deep diabetic coma. He therefore, advocates the use of sodium bicarbonate in the long continued acidosis, where the alkali reserve has been greatly reduced. He recommends 1 gram per kg. body weight per hour as the maximum dose. He also warns to be on the lookout for alkalosis and recommends frequent check up on the urine and blood. He feels that when an alkaline urine is gotten, alkali therapy should be stopped. Also by taking frequent CO_2 combining power estimations and not allowing the CO_2 to rise above 40 vols. per cent alkali therapy is made perfectly safe.

No one, however, believes that alkali alone will do the work, since the basic difficulty is a ketosis, while the dehydration is secondary. Hence salt solution, best given in Ringer's solution, and soda bicarbonate should be supportive rather than primary. A method of treatment is given with the presentation of cases..

NON DIABETIK KETOSIS

VIII

Post Operative Ketosis

Many clinical men have recognized a transient form of "acidosis" in infancy and childhood which simulates diabetic ketosis. It has also been known that acidotic tendencies are of greater occurrence in early life. Because the normal blood of infants differs somewhat in its chemical composition from that of adults, containing about 10% less electrolyte and protein (Hartmann), and because serious acidotic changes are frequently encountered in certain diseases of infancy and childhood; an adequate knowledge of normal blood chemistry is apparent.

Bakwin (1922) has shown an increased concentration of blood plasma in normal new born infants. The increase in osmotic pressure is not only present in the blood but other tissues as well. They interpreted the higher osmotic pressure as being due to the loss of water and subsequent dehydration as is born out by the initial weight loss.

Hoag and Kiser (1931) showed that the serum of the new born infant has a lower CO_2 content and a higher chloride content than that of normal adults. They studied a series of 73 cases of normal new-born infants from 8 to 13 days of age, all were breast fed, received accessory fluids, and were free from abnormal symptoms. The following averages were obtained:

Table II

CO ₂ content of serum -----	7.42
pH of serum -----	54.5 vols. percent
NaCl -----	62.1 mgm percent
Base Bicarbonate -----	23.4 millimoles per l.
Base chloride-----	106.2 Millimoles per l.

Marples and Lippard (1932), in considering the low alkaline reserve of the new born infant, point out that infants and children have a tendency toward an acidotic condition. They found a gradual increase of chlorides, beginning the first day after birth and reaching its maximum on the third day. This, they claim, is parallel with the decreased loss of weight as a result of fluid loss. Hence they ascribe the high chloride content to increased concentration of the blood plasma. There is apparently not sufficient water to eliminate the access chlorides. These chlorides, therefore, replace the base bicarbonate reducing the alkali reserve of the blood. The infant attempts to compensate for the lack of fluids by water retention. Oliguria is thus a common occurrence during the first few days of life. As water is furnished to the infant the chlorides are gradually reduced and the alkali reserve rises. But, according to Marples and Lippard, it does not reach the adult figures until the child is about two years old. They also feel that starvation during the first few days of life partially account not only for the weight but the accompanying acidosis. This has been supported by the earlier work of Gamble, Ross and

Tisdall (1923).

This preliminary discussion not only serves to contrast the apparently normal and pathological conditions in infancy and childhood, but also serves to visualize that the abnormal is many times an exaggeration of symptoms found in the normal child.

Brewer in 1902 described a fatal case of acetonuria following an operation for acute appendicitis. Treatment with salts and soda bicarbonate was without effect.

Brackett, Stone and Law (1904) reported 7 cases of acetonuria in children due to malnutrition. They claimed that it is due to a lack of carbohydrate and concluded that aciduria associated with death after anesthesia is due to the pre and post operative starvation diet. They, therefore, recommend adequate preparation for major surgical operation, including administration of carbohydrate and alkali.

Beven and Favil (1905) reported a post-surgical death of a 12 year old girl, after the administration of chloroform anesthesia. Autopsy findings showed degeneration of the parenchymatous organs, particularly the liver. They believed that liver changes resulted from alkali and carbohydrate depletion within the organ.

Brown (1911) reported 2 cases of post anesthetic acid intoxication in children, both ending fatally. He drew atten-

tion to the necessity of examining the urine for acetone and diacetic acid in all patients for operation and that operation should be postponed, if possible when acetone bodies are present in the urine. He recommended preoperative administration of glucose and soda bicarbonate, being of the opinion that such preoperative treatment tends to reduce post operative vomiting--hence eliminating starvation ketosis.

Russ (1913) reported five cases of post operative ketosis in children. Three of his cases died in 24 hours after operation. He believed the disturbance was due to a reduction in the alkali reserve of the blood and to a metabolic disturbance provoked by the operation. In two of his cases ketosis was present before operation. In these cases operation was postponed and ketosis removed by a high carbohydrate diet and by a liberal supply of fluid and alkali. Operation was then performed without serious disturbance.

The classical experiments of Cfile (1915, 1915a 1918) is known to every clinical man. In his work on dogs he showed an increased pH of the blood in great exhaustion resulting from infection, injury, shock, starvation, or hemorrhage. Moreover, he showed that a general anesthetic when given to dogs in any one of the states given above will invariably result in death. He found that when morphine precedes the anesthesia, not only less of the anesthesia need be used but the pH was higher than animals who did not receive morphine, except in acidotic dogs

where morphine decreased the pH of the blood séum. In a later article (1918) he confirmed his belief by subsequent studies. He further states that the adrenal gland and liver are in some way related to the regulation of the acid base-balance, such function is disturbed in conditions noted above.

He believed that the ideal treatment of the class of patients handicapped by exhaustion, in whom acidosis is present or is threatended, to be

1. The preoperative administration of sodium bicarbonate and of bromides by rectum
2. "Twilight" anesthesia
3. Complete anociation by the use of local anesthetics and gentle manipulations so that but a small amount of the anesthetic is needed.
4. In bad risks as rapid a technique as is consistent with good work, to shorten the periods of anesthesia
5. The avoidance of worry, fear, injury, since those factors produce a fall in the pH of the blood.

He emphasized that post operative acidosis is necessarily a ketosis, resulting from the destruction and increased metabolism of the body tissues and to starvation. His experiments led the way to numerous experimentation and practical application.

Thalheimer (1923) was first to administer and recommend insulin in combination with glucose in cases of postoperative acidosis and ketonuria. He presented 3 cases with symptoms of

acidosis yielding to treatment with intravenous glucose injections with insulin. He believed that ketosis occurred when the organism lacks carbohydrates or when the carbohydrate metabolism is subnormal--a condition simulating, in part at least, diabetic ketosis. In post operative acidosis glucose plus insulin seemed to be more efficient than the use of insulin or carbohydrate alone. He, therefore, recommended the use of insulin in post operative acidosis along with fluids and glucose. His work was later confirmed by Fisher and Suell. Their treatment consisted of intravenous injection of 500 cc of 10% or 1000 to 2000 cc of 5% glucose solution and 15-20 units of insulin immediately afterwards. They emphasize the necessity of injecting glucose before injecting insulin to give patient an excess carbohydrate reserve. They claim that insulin and glucose is almost specific for pre and post operative ketosis. As in case of diabetes, they warn against overdosage.

Wumer (1926) has done an immense amount of experimental work on dogs and rabbits as well as human subjects on narcosis acidosis. The examinations showed that ether narcosis in all the cases provoked a fall in the alkali reserve of the blood. This fall was compensated in the course of 24 hours and followed by an increase in the alkali reserve. Immediately after narcosis acidity of the urine as well as ammonia showed a marked increase, but gradually turned back to normal in 24-48 hours. Ketone bodies were not found in all cases studied, but evidence of other organic acids was noted. He concluded that the narcosis effect on acid-base balance of the blood is due to an:

1. Immigration into the blood of pathological acids which

bind alkali and consequently bring about a fall in the alkali and consequently bring about a fall in the alkali reserve.

2. Influence on the central nervous system, by reduction of the activity of the respiratory center, owing to the narcosis, the consequence of which is a fall in the pH of the blood.

compensation is brought about by renal and respiratory, and by the ability of the living tissues to produce ammonia. In his opinion acidosis has a stimulating effect on the respiratory center whose irritability is reduced by the narcosis, serving as a compensation for the ketosis which is usually mild.

Rocher (1933) gives a very good review of acidosis due to narcosis. He also emphasizes that the condition is primarily a ketonemia. He attaches very little significance to post operative ketosis in adults, but calls the surgeon's full attention to operations performed in children. In an elaborate series of experiments he showed that post operative ketonuria is more pronounced in general than local anesthesia. His findings agree with that of Wumer. In addition he found a decreased excretion of salts from the body and accounted for it by the scanty preoperative diet. He also showed a post operative hyperglycemia (50-80%) as an almost constant finding immediately after general narcosis. The sugar level became normal 24-48

hours after operation.

It is evident from the work of the men noted above that post-operative acidosis is not a common occurrence even in childhood, especially when adequate preoperative care has been given. The etiological factor is probably a group of condition, such as anoxemia (especially when the closed ether mask is used), starvation or hunger acidosis pre and post operatively, tissue injury may help in producing organic acids, incapable of being oxydized, and loss of fluids due to vomiting would still further complicate the picture.

A rational form of treatment would be:

1. To eliminate all forms of anxiety, fear and exhaustion prior to operation
2. To furnish adequate nutrition, both pre and post-operatively.
3. To operate quickly and efficiently, where acidosis is threatened, causing as little injury to tissues as possible.
4. Antiacidotic treatment is indicated only where acidosis is feared. Such treatment should consist of glucose, saline and much fluid. The saline is especially indicated where minerals have been lost as a result of vomiting. Insulin should be given in small doses when ketosis is apparent.

McCrossen (1929) advocates the use of glucose plus insulin

injected into the peritoneum in the case of infants when administration of glucose by mouth is not possible. He emphasizes that time is a big factor in acidosis of children, since more can be done early than late. He recommends the use of 500-800 cc of 10% glucose with every unit of insulin when given slowly there is less danger of overloading the heart.

McCrossen believes that alkali therapy is not indicated in the mild type of acidosis. However, in the long drawn out cases ~~where~~ the bicarbonate should be given. Following the table of Palmer and Van Slyke (p. 22) he recommends one gram perkg. body weight.

McCrossen also calls attention to the great hazard of surgery in diabetic patients whose surgical risk is already increased by his potential ketosis. He feels that the surgeon who has time to prepare the diabetic patient is capable of rendering that patient comparatively safe.

Post-operative patients who show signs of acidosis should have aside from the routine laboratory work a determination of the alkali reserve. Treatment would depend on such findings and whether or not there is a history of improper food, vomiting, starvation or dehydration.

The last two conditions may be combated by giving the patient plenty of fluids and sufficient carbohydrates. Many surgeons recommend stick candy and orange juice when such can be taken by mouth. If this is not retained 10% glucose solution

and 3-5% soda solution may be given per rectum by the Murphy drip (McCressen). Injections of saline (Ringer's sol.) supplemented by glucose given intravenously either with or without insulin. When vomiting is present washing out the stomach and leaving a small stomach tube for feeding purposes is often of great value.

IX.

G A S T R I C D I S O R D E R S

In diseases of the gastro-intestinal tract acidosis as well as alkalosis may occur. The former is associated with the various diarrheal conditions, the latter with persistent vomiting as in recurrent vomiting of childhood, pyloric stenosis or upper intestinal obstruction. It is often of extreme importance to recognize whether an alkalosis or an acidosis actually exist.

Czerny(1897) is believed to be the first to describe the alteration in the character of respiration in nutritional conditions. He called attention to the resemblance between the respiration of infants dying of gastro intestinal disease and that of rabbits poisoned with mineral acids(Walters). He believed that in the diarrheal diseases of infancy there may rapidly develop a severe and usually fatal acidosis apparently not due to acetone bodies.

Steinitz(1903) determined the minerals lost by the intestines during an attack of diarrhea in infants and children. He found a great increase of minerals in the stools, especially of sodium. He theorized that the acidosis is only relative, inasmuch as it was not due to an accumulation of acids, but to loss of base. He emphasized the danger encountered in the long continued loss of base as a result of the prolonged diarrheas of childhood.

Hewland and Marriott(1916), in explaining the hyperpnea encountered in severe diarrheas, suggested that there is an increase in the Hydrogen ion concentration of the blood causing a marked stimulation of the respiratory center. They studied a large number of cases, using a large number of tests in determining the pH of the blood, and found acidosis in most cases of

severe diarrhea. They believe that the acidosis is not due to a ketosis but to aphosphate retention in the blood.

MacAdam and Gordon(1922) found acetone and diacetic acid in the urine of children suffering from recurrent vomiting. Blood chemistry showed an increased pH, an uncompensated CO₂ deficit. They warn against assuming an acidosis when ketonuria is present .

Myers and Booher(1924) reported several cases of high alkali both compensated and with high pH following the Sippy treatment for peptic ulcer. They also write:

We are inclined to think that alkalosis is a condition overlooked and sometimes confused with acidosis by clinicians. We believe that great care should be emphasized in administration of alkali.

Hartmann(1928⁹) stated that when vomiting occurs in an otherwise healthy child because of pyloric stenosis, the result is loss of HCl, base, chloride, and water from the body. The HCl far exceeds the loss of BCl, leading to retention of base bicarbonate(alkalosis). However, Marriett and Davidson(1923) have shown that in febrile children considerable less HCl is secreted in the stomach after feeding. Hence one should not expect a great reduction in the chloride content of the blood when vomiting resulted from infection as when present in association with obstruction. Vomiting associated with infection especially where a focus of infection may be detected is, therefore, not likely to cause marked loss of chloride ion.

Hamilton, Laslo and Meeker (1929) reported eleven cases of severe acidosis in a series of 25 cases of the non-specific type of acute diarrhea. The most common change in the blood was a decrease in the concentration of fixed base. The acidosis when present was invariably a chloride acidosis. They noted two types, one with a normal low base content of plasma with the chloride not being decreased in proportion to base and one with a normal or high base content, chloride being increased even more than the base. They concluded that the cause of acidosis is a relatively greater loss of base from the stool bound as the salt of a weak acid and not compensated by loss of from the stomach by vomiting.

It has long been known that diarrhea in infancy and childhood is associated with marked dehydration. This is unquestionably due to the loss of fluid by Bowel, by vomiting and by the physiological overactivity of the kidney and sweat glands to eliminate toxins in the body due to disease. In case of severe diarrhea most of the fluid is lost by the bowel and through the vomitus. To compensate for such marked loss of fluid an oliguria is commonly found. The clinical picture of acidosis of severe diarrhea is well described by Schultz (1933):

The infant is found to have some focus of infection either in the gastrointestinal tract itself or in the throat, ear or mastoid antrum. Unless extremely prostrated, irregular fever is present. Vomiting of greater or less severity occurs and from 8 to 20 copious watery stools are passed daily. Urinary output is greatly reduced. There is increasing restlessness and the infant becomes rapidly dehydrated, with a dusky gray color to the skin. Presently

the characteristic air hunger type of respiration is noted and the infant may rapidly become comatose.

Gamble (1928) described the chemical blood findings in infants suffering from diarrhea (dysentery). He claimed that there is a relatively larger withdrawal of fixed base than of chlorine, causing a reduction in the bicarbonate. The contents of the stool agrees with the loss of substance from the plasma. The most striking change is the reduction of bicarbonate as determined by the CO_2 combining power of the blood plasma. There is usually a considerable increase of lactic acid ions, due to the dehydration and resulting anemia from circulatory embarrassment. His chart (No. 2) will serve to illustrate changes in the bicarbonate made necessary by a group of diseases characterized by vomiting, diarrhea and dehydration. In addition during such periods evidence of kidney damage may be found with considerable amount of albumen and large number of casts in the urine. There may also be a diminished urinary acidity and ammonia concentration relative to the concentration of fixed base. Hartmann (1929) noted in severe forms of watery diarrhea loss of fixed base through the bile. This would tend to further decrease the "fixed" base.

Aside from the failure to replenish minerals lost from the body in the stool and urine, starvation due to the presence of vomiting will cause more rapid destruction of body tissues

with increase liberation of such acids (relative to fixed base) as phosphoric and sulphuric. In addition the organic ketone acids may accumulate if carbohydrate starvation becomes sufficiently pronounced. According to Hartmann (1929) ketosis is much more commonly associated with bacillary dysentery than is with diarrhea of the cholera infantum type (also called "alimentary intoxication", non specific diarrhea, summer diarrhea).

The etiology of acidosis in such conditions may be outlined as follows:

1. Extensive loss of body water-- resulting in
a n h y d r e m i a

a. Also called alimentary intoxication, ileocolitis, cholera infantum.

b. Reduction in blood volume, with a subsequent decrease in blood flow through vital organs-- respiratory center-- leading to anoxemia, which favors accumulation of lactic acid and diminution in urinary secretion, favoring retention of anions (as Cl^- , HPO_4^- and SO_4^-). Increase in these ions occurs largely at the expense of H_2CO_3 which is displaced from the combination with base (BHCO_3). This will in turn increase the pH.

2. Loss of body salts.

a. Due to failure of water reabsorption by the

intestines.

b. By way of the G.I.T., less often by way of the kidneys.

3. Starvation acidosis

- a. Rapid destruction of body tissues
- b. Carbohydrate deficiency.

Based on the foregoing conception of acidosis in severe diarrhea the logical form of treatment would seem to be:

1. Wherever possible, to remove the cause of the diarrhea.

2. To restore blood volume by replacing fluids lost.

This would help oxidize and remove the excess of lactate ion, releasing base for combination with carbonic acid. This would also help to produce diuresis, so that accumulated inorganic ions as phosphate, sulfate, and chloride may be excreted in combination with ammonia and thus release base for the restoration of base bicarbonate.

3. In more severe case restoration of salt lost by bowel and kidneys.

~~Other~~ Administration of fluids often fails to relieve the dehydration and anhydremia, because of the associated vomiting and the diarrhea. Parenteral administration of normal physiological salt solution should, then be resorted to.

When severe watery diarrhea persists, however, salt solution administered alone will not suffice to relieve the marked

acidosis, if anhydremia, oliguria with renal insufficiency persist. Moreover, in such cases the osmotic pressure of the blood is already high, often as high as 90 mgms. per cent (Hartmann, 1929), increase in salt concentration would result in further loss of BHCO_3 . The urine may become more alkaline, thus simulating an alkalosis, although the pH of the blood is much lower than normal.

According to Hartmann isotonic salt solution possesses some advantages over physiological saline in acidosis of severe diarrhea. The solution can be stored as glycogen or oxidized to furnish energy and relieve ketosis if present. It does not tend to permanently raise the osmotic pressure. The combined use of physiological salt and glucose is, according to McCrossen often more effective in producing diuresis than is the administration of either one alone. He recommends 10-20% dextrose solution following intraperitoneal injection of saline. Both solutions need to be sterile and chemically pure in order to prevent irritation.

X

FAULTY ELIMINATION

Since the chief excretory channels of acids from the body is chiefly by way of the lungs and kidneys, it seems only logical to infer that impairment of any one of these organs would lead to an acidosis. Space does not permit a lengthy discussion of each of these regulating agents, theoretical considerations must of necessity be omitted.

Barach, Means, and Woodwell (1922) observed a tendency to a lowering of the alkali reserve in pneumonia. They found in 10 cases an average CO_2 capacity in arterial blood at 40mm. pCO_2 at 37°C . of 43.2 vols. per cent as compared with the average for normal individuals of 49.3 vols. per cent. The lowest observed was 35 vols. per cent. They also calculated the arterial pH from the CO_2 absorption curve and obtained an average in their 10 cases of pneumonia of 7.31 with 4 cases below 7.3. The lowest pH observed was 7.2. However, they found no relation between pH, reduction of alkali reserve and the prognosis or degree of toxemia. They observed a spontaneous rise in the alkali reserve with a return of the pH to normal at or shortly after crisis. In one case studied restoration of a normal pH was obtained with crisis, after vigorous oxygen therapy.

Hastings, Neill, Morgan and Binger (1924) studied a series of 30 pneumonia patients, making direct determinations of the pH and CO_2 concentration of the blood. They showed a lower arterial CO_2 tension during febrile periods than after return to normal temperature in seven cases. However, pCO_2 and increased O_2 unsaturation did not occur with sufficient regularity to indicate a causal relationship. The alkali reserve

and pH ~~were~~ within or near normal limits in every case, the pH in most cases being in the alkaline half of this range (pH 7.3 to pH 7.5). Their results contraindicate alkali therapy in all cases studied. Moreover, they found edema occurring during convalescence from pneumonia in association with sodium bicarbonate administration. Their experiments tend to show that acidosis of pulmonary pathology is primarily an oxygen deficiency. Hence, oxygen and not alkali is the proper type of therapy, as is born out by clinical observation.

Hewlett (1928), in reviewing the acid-base disturbance as it is found in pulmonary pathology states:

It seems probable that no constant disturbance of acid-base equilibrium occurs and that its status in a given case is determined by the relative influence of a number of variable factor, among which are, extent of lung involvement, the amount of flow through the unsaturated lung, the condition of the myocardium and the response of the kidneys.

It should be apparent that impairment of renal activity would invariably result in the excessive accumulation of products of metabolism. Organic and inorganic acids combine with ammonia and are excreted through the kidneys. It may be inferred that impaired renal function would induce an acidosis.

R. von Jacks (1883), by titrating the ash of blood first demonstrated a diminished alkalinity of the blood of uremics.

Sellards (1912) and Palmer and Van Slyke (1917) showed that the depletion of the alkali reserve could better be gauged by noting the amount of alkali that must be administered to cause

excretion of a less acid urine rather than of an alkaline urine. Their experiments have already been reviewed (p.23).

Peabody (1915) showed that there was no strict parallelism between the other evidences of impairment in renal function and the degree of acidosis, but only a general tendency to become marked in advanced cases of chronic diffuse nephritis. The dyspnea of the cardiorenal disease also was commonly more marked than could be accounted for merely by the acidosis.

Howland and Marriett (1916) demonstrated an increase in the phosphate of the serum in nephritis with lowered CO_2 capacity of the plasma and with decreased plasma pH. According to Austin and Cullen (1926) their work has been confirmed by numerous investigators. The quote Means and Rogers (1917) who reported an extreme acidosis in a man with bilateral polycystic kidneys, complicated by a septic infection of the hand. Two days before death he had extreme hyperpnea with ventilation of 51 liters per minute, an alveolar CO_2 pressure of 6.4 mm., a blood urea of 3.32 mgm per 100cc (55mm), a CO_2 capacity of the plasma of 12 vols per cent (5.4mm), and a s e r u m p h o s p h o r u s of 18 mgm per cent (5.8mm), and serum calcium of 3 mgm. per cent. At this time 110 grams of NaHCO_3 by mouth failed to render the urine alkaline. Austin and Cullen believe, however, that some other factor appears to be concerned here than merely a phosphate retention.

MacNider (1920) has shown a definite acid-base disturbance in experimental nephritis in animals. He demonstrated improve-

ment in renal function when the disturbance of acid-base equilibrium is corrected by alkali therapy. He showed that there is a diminished susceptibility of the kidney to injury by toxic substances when by alkali therapy the acidosis is prevented.

Osman (1930) in an interesting review of alkali therapy of chronic nephritis states::

Alkalies should never be used except with some specific object in view. The frequent practice of giving "small" doses in the hope of that they "might do some good" is bad medicine and should be condemned.

He found that 84% in a series of 100 cases of all types of chronic nephritis there is a decrease in the plasma bicarbonate, hence supplying such a deficiency seems to him good practice. The value of such alkali, he believes, lies in its action as a diuretic thus increasing the excretion of retained acids. He also found that albumenuria and edema is reduced with alkali therapy. This is of interest since albumenuria depletes protein in the blood decreasing the oncotic pressure, resulting in edema.

He recognized the dangers of alkali therapy, claiming that it should not be given when there is evidence of severe kidney damage, or when there is evidence of an alkalosis, especially tetany. He recommends calcium with alkali treatment, claiming that it prevents the occurrence of tetany. He gives the following indications and contraindications for the use of alkalies in nephritis:

A-- Indications:

1. Where blood estimation shows a low plasma bicarbonate
2. In production of diuresis in control of edema in
 - a--Chronic parenchymatous nephritis
 - b--Chronic mixed nephritis
 - c--Late stages of acute parenchymatous nephritis.
 - d--Late stages of subacute nephritis with persistent edema and with marked hematuria.

B-- Contraindications:

1. In early stages of acute nephritis with hematuria as in
 - a--Acute nephritis (Hemorrhagic or diffused type)
 - b--During acute exacerbations with hematuria
 - c--In the presence of marked myocardial degeneration and cardiac arrhythmia
 - d--In dyspnea and vomiting without estimation of blood bicarbonate.

Fischer (1921) discusses the subject from a chemical point of view. Basing his arguments on extensive experimentation in vitro, he concludes that alkalies should be used in nephritis with edema. "The addition of a salt to an acid or alkaline medium causes dehydration of tissues in proportion to the concentration of the salt." Similarly, Fischer upholds the colloid-chemical theory in regard to hydration and dehydration of lyophilic colloids. He believes that edema is a problem of colloid chemistry-related to the osmotic and onkotic pressure of body fluids. He states:

A state of edema is produced whenever in the presence of an adequate supply of water, the capacity of the tissue colloids for holding water (osmotic pressure) is increased above that which we call normal.

Such a condition is brought about either by an accumulation of acids within the tissues due to their inadequate removal, or by the retention of urea pyridin, amines which hydrate colloids as do acids.

He believes in giving substances that will dehydrate body fluids by the simple process of osmosis. He correctly argues that dehydration of tissues in diabetes is due to an increased osmotic pressure. Moreover, he believes that the very changes in the kidney in nephritis are primarily colloid chemical in nature, the result of an accumulation of acids in the organ and not in other tissues of the body.

In addition to reverse changes of osmotic pressure in pathological kidney, the organ needs oxygen for proper excretion. Fischer claims that caffeine^{and}, digitalis acid in restoring oxygen supply to the kidney and acts as ~~x~~ diuretics.

Fischer concludes that in the treatment of nephritis the aim must be to avoid and remove as far as possible every condition that favors abnormal production or accumulation of acid in the kidney, or of other substances which in their effect on tissue colloids behave like acids. The rule to follow is to give alkali, salts, and sugar and to control the intake of water. He advocates alkalies to neutralize

the accumulated acids, salts and sugar to increase the osmotic pressure of the blood. The sugar also helps to burn up incompletely oxidized organic acids, since these are formed because of a carbohydrate deficiency (starvation acidosis).

He recognizes the advantage of an alkaline diet in the chronic type of nephritis, but not a low salt diet. This idea seems to raise much objection among clinical men who are convinced that a low salt diet is essential in chronic nephritis.

Lyons (1931) also advocated the use of an alkaline diet. He claimed that in a normal diet the acid overbalances the basic elements. Hence, the diseased kidneys may be lightened by diet which on oxidation leave an alkaline rather than an acid residue. Sansum, Blatherwick and Smith (1923) reported clinical improvements in 90% of their cases of the arterial hypertensive type of nephritis.

In Ryon's cases, a highly basic diet in chronic interstitial nephritis caused an increase of the CO_2 combining power of the blood, a decrease in the acidity of the urine and NPN of the blood. He believes that the alkaline diet helps to an improved utilization of proteins, so that only a minimal amount is necessary for body metabolism.

Morgulis (personal communication) is in full agreement with such findings. He states that on an alkaline diet the ammonia is brought to its end stage urea and does not stop short in the process, by excreting ammonia or its salts. He emphatically opposes alkali therapy in any type of prolonged acidosis, saying that in most cases other measures, such as

glucose, insuline and salts are much better. Levine(1930) has listed a number of acid and alkaline foods. These may be found in any text book on nutrition.

In summarizing the acidosis of renal disease, one is aware of the variability of opinions, as given above. This may be due to the fact that not only is the clinical picture variable but also the blood findings. Briefly stated, the later stages of severe glomerular or diffused nephritis is almost always characterized by a marked acidosis. It tends to persist and may be the only kind which is difficult to diagnose clinically (Hartmann 1928). The chief cause for reduction of bicarbonate in the blood is the renal insufficiency operating in such a way as to retain excess acids with excessive loss of base (Hartmann and Darrow, 1928^a). Both organic and inorganic acids may be retained. Loss of base occurs as a result of progressive inability of the damaged kidneys to substitute ammonia for fixed base. Hence the urine need not be acid even in a severe form acidosis of chronic nephritis. BCl is reduced in the blood (Hartmann and Darrow 1928^d).

Intervening symptoms may tend to change the clinical picture to some extent, such as vomiting, diarrhea, "uremic" convulsions or circulatory failure.

All these conditions must be treated symptomatically. Vomiting, for example, may give an alkalosis in the presence of prolonged kidney pathology; alkali therapy in such cases

would only make a bad condition worse. Ammonium or calcium chloride would in this case be better treatment.

Again, Hartmann (1929) has shown that mild acidosis in nephritis, not only seems to do little harm but seems to be of some value in preventing symptoms of tetany. This may explain on the basis of a high serum calcium associated with acidosis.

The high serum calcium tend to decrease the phosphate of the blood-- a result hoped for in chronic nephritis. Adequate treatment would therefore be to reduce acid excretion to a minimum and to increase fixed base intake. The former may be accomplished by giving isotonic glucose, the latter by a high alkaline diet. Only in the very severe cases should alkali be used, but not for prolonged use. Reduction of acids especially organic would in itself tend to increase the base carbonate of the blood.

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Finis

S U M M A R Y

It was the chief aim of this paper:

1. To emphasize the extreme constancy of reaction of the living body. It should be evident from the description of the normal physiology of acid-base regulation that there is a highly complex mechanism in the body which tends to keep the reaction within normal limits. It has also been stressed that such constancy of reaction is even more carefully guided than temperature.

2. To emphasize the possibility of greater change in children than adults. This has been definitely shown by the greater frequency of acidosis in infancy and childhood.

3. To correlate normal with pathological function. Since disease is a disturbance in physiology of the organism, most often an exaggeration of the normal, it can best be understood when the mechanism of the disturbance is known. This is done by contrasting normal and pathological physiology.

4. To apply a rational form of treatment. This paper attempts, to emphasize that alkali treatment should not be given at random when acidosis is suspected. Each condition must be studied as to the possible blood changes which may take place. This should be verified by blood chemistry.

This, of course, is difficult where equipment is not available. Extensive alkali therapy is indicated only when severe acidosis especially of a prolonged nature is evident. Such cases are usually hospital cases, and to my opinion all hospitals should have available technicians to carry out at least some of the tests mentioned.

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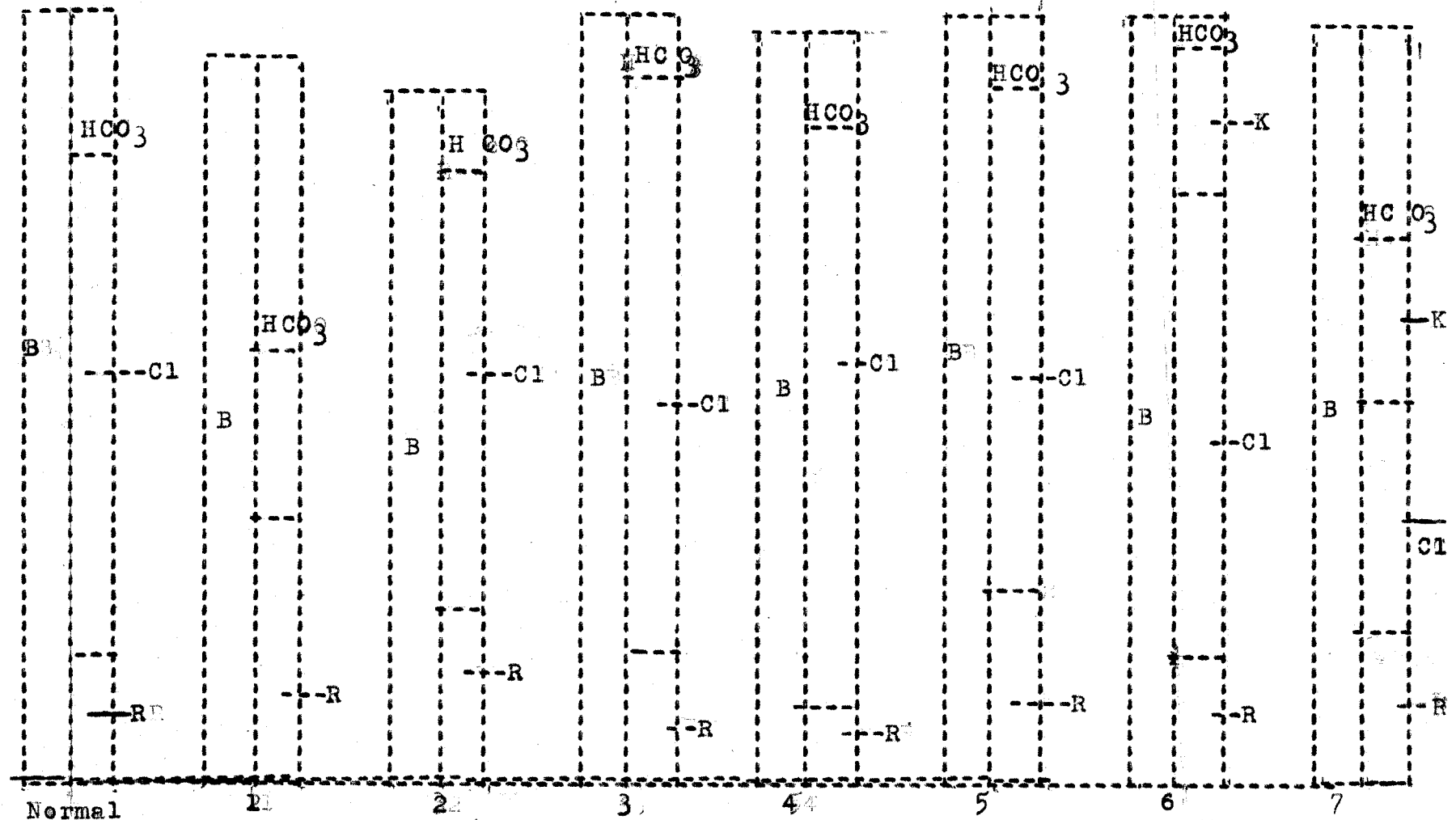


Diagram showing various defects in acid base structure of the blood plasma and the necessary change in bicarbonate. No. 1 alkalosis of pyloric obstruction. No. 2 acidosis caused by diarrhea. No. 3 CaCl_2 acidosis. No. 4 Chloride acidosis in tubula nephritis. No. 5 Retention acidosis in glomerular nephritis. No. 6 Acidosis due to ketosis; diabetes No. 7 alkalosis in the presence of ketosis; upper base)B), chloride ion (Cl^-) and bicarbonate ion (HCO_3^-). The smaller acid factors were not individually measured; they are all contained in the remainder (R).

From Gamble (1928)

P R O T O C O L (1)

CASE: Eddie S.

Clinical symptoms of diabete mellitus were first noted in 1924, when the patient was 6 years of age. During his first hospital admission in July, 1924, he was found to be a moderately severe diabetic, but otherwise normal, and did well while in the hospital. After discharge, dietary indiscretions were frequent, and occasionally, for one reason or another, insulin was with-held or given inadequately, and acidosis requiring hospital treatment resulted. During such periods abdominal pain referred to the right upper quadrant as a rule, vomiting and leucocytosis were marked. Fever or other evidence of infection were never present, and almost immediate relief of all symptoms followed recovery from acidosis.

Therapy, bearing on the results shown in the tables, follows :

A D M I S S I O N on Sept. 16, 1926 (Table 1)

12:00 Noon Insulin 50 units, intravenously

1:30 P.M. Insulin 20 units, subcutaneously, orange juice and water by mouth, ad. lib.

8:00 P.M. Insulin, 20 units subcutaneously.

11:00 P.M. Insulin, 20 units, subcutaneously.

11:00 P.M. Orange juice 200cc plus 40 grams cane sugar.

4:00 A.M. Insulin 10 units, subcutaneously.

1. From Hartmann and Darrow (1928).

Sept. 17, 1926

5:00 A.M. Orange juice 200cc + 40 grams cane sugar.
12:00 noon Insulin, 10 units subcutaneously.
4:00 P.M. Insulin 15 units, subcutaneously.

Sept. 18, 1926:

Regular diet. Exact insulin requirement not yet ascertained.

A D M I S S I O N of April 15 1927 (Table 3)

April 15, 1927

11:00 A.M. Insulin 50 units intravenously
11:00 A.M. Ringer's solution 450cc intravenously.
1:15 P.M. Insulin 30 units, subcutaneously
6:00 P.M. Insulin 15 units, subcutaneously
12:00 P.M. Insulin 15 units subcutaneously.

A D M I S S I O N of April 3, 1928 (Table 3)

April 3, 1928

11:45 A.M. Insulin 40 units, intravenously
11:45 A.M. Insulin 40 units, subcutaneously
11:45 A.M. 7.5 per cent glucose solution, 400cc,
intravenously
3:00 P.M. Insulin, 50 units subcutaneously
4:00 P.M. Ringer's solution by Murphy drip per rectum.
9:00 P.M. Insulin 15 units subcutaneously

April 4, 1928

3:00 A.M. Insulin, 15 units, subcutaneously

9:00 A.M. Meal: B 20 F 50, CH 20.

9:00 A.M. Insulin 20 units, subcutaneously

12:30 P.M. Meal as above

12:30 P.M. Insulin 15 units subcutaneously

6:00 P.M. Meal as above

6:00 P.M. Insulin 15 units, subcutaneously

April 5, 1928

Meals and insulin as on April 4, 1928.

A D M I S S I O N of June 6, 1928 (Table 3)

June 6, 1928

11:45 P.M. Insulin 50 units intravenously

1:00 A.M. 500cc 5% Glucose solution, containing 12.5 grams.

NaHCO_3 and 15 units of insulin, intravenously.

June 7, 1928

11:30 A.M. Ringer's solution 400cc intravenously.

1:30 A.M. Insulin 20 units subcutaneously

9:00 A.M. Previous diet and insulin dosage resumed.

D I S C U S S I O N

1. In case 1 on Apr. 3, 1928 (Table 3) the water content of the first sample of serum was 88.6 and the true plasma concentration 7.88 grams per cent by volume, while after complete recovery on April 6, 1928, the water content increased 93.9 and the protein fell to 6.34%. This indicates the marked de-

hydration in diabetes as evidenced clinically by the dry skin, dry tongue, sunken eye balls, etc. (McCressen, 1929).

2. Despite the anhydremia, the concentration of total base tends to be slightly below normal, also found by Peters, Bulger, etc.

3. The sum of the most important normal acids ($\text{Cl}^- + \text{HCO}_3^- + \text{protein}^- + \text{HPO}_4^- + \text{lactate}^-$) is always below normal and in some instances extremely low, while the undetermined acid is always extremely high. Such undetermined acid presumably is diacetic acid (Hartmann & Darrow).

4. BHCO_3 and pH is often extremely low.

5. Of the remaining acids chloride is most regularly affected, sometimes by as much as 20mM. Lactic acid is often increased, HPO_4 is slightly elevated but not significant from standpoint of base binding capacity.

6. From the osmolar viewpoint, there is a marked reduction in total electrolyte, with an increase in glucose sufficient to maintain a normal osmotic pressure.

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